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Transcutaneous monitoring as a replacement for arterial PCO_2 monitoring during nocturnal non-invasive ventilation☆

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Summary
Background: Continuous, non-invasive assessment of alveolar ventilation achieved by transcutaneous PCO_2 ($PtcCO_2$) monitoring is clearly superior to intermittent, invasive blood gas analyses in patients receiving nocturnal non-invasive positive pressure ventilation (NPPV), but the reliability and accuracy of $PtcCO_2$-monitoring is still disputed. The present study was aimed at investigating the capability of modern $PtcCO_2$-monitoring to reliably assess alveolar ventilation during nocturnal NPPV.
Methods: Capillary blood gas measurements (11pm, 2am, 5am and 7am) and 8 h of continuous $PtcCO_2$-monitoring using three of the latest generation devices (SenTec Digital Monitor, Radiometer TCM4-TINA and Radiometer TOSCA500) were performed during polysomnography-proven sleep studies in 24 patients receiving NPPV (15 with COPD, 9 with restrictive disorders).
Results: The technical calibration drift for SenTec DM, TCM4-TINA and TOSCA500 was 0.1, −0.4 and −0.5 mmHg/h, respectively. Bland-Altman method comparison of $PaCO_2$/drift-uncorrected $PtcCO_2$ revealed a mean bias (limits of agreement) of 1.0 (−4.7 to 6.7), −1.5 (−15.6 to 12.5) and 0.8 (−6.8 to 8.3) mmHg, respectively. Continuous overnight $PtcCO_2$-monitoring detected variations in alveolar ventilation, with median ranges of 12.3 (10.7–14.5) mmHg

Abbreviations: ABG, arterial blood gas analysis; BE, base excess; BMI, body mass index; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CO_2, carbon dioxide; EPAP, expiratory positive airway pressure; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HCO_3^-, standard bicarbonate; HRF, hypercapnic respiratory failure; IPAP, inspiratory positive airway pressure; LTOT, long-term oxygen therapy; min, minutes; NF, normality test failed; NREM, non-rapid eye movement sleep; NPPV, non-invasive positive pressure ventilation; PCO_2, partial pressure of carbon dioxide; $PaCO_2$, arterial partial pressure of carbon dioxide; $PetCO_2$, end-tidal partial pressure of carbon dioxide; $PtcCO_2$, transcutaneous partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; REM, rapid eye movement sleep; RM-ANOVA, Repeated Measures Analysis of Variance; RR_{set}, preset respiratory rate; RV, residual volume; SaO_2, arterial oxygen saturation; SenTec DM, SenTec Digital Monitor; SD, standard deviation; TLC, total lung capacity; TST, total sleep time.

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for SenTec DM, 14.5 (12.5—17.0) mmHg for TCM4-TINA and 11.5 (11.0—13.0) mmHg for TOSCA500 (RM-ANOVA, $p < 0.001$). The four capillary $PaCO_2$ values ranged by a median of 6.3 (4.7—9.7) mmHg.

Conclusions: Modern $PtcCO_2$-monitoring is reliable, accurate and robust. Since $PtcCO_2$-monitoring is also non-invasive, does not disrupt sleep quality and provides a more complete picture of alveolar ventilation than intermittent capillary $PaCO_2$, $PtcCO_2$-monitoring should become the preferred technique for assessing alveolar ventilation during nocturnal NPPV.

Trial Registration: DRKS00000433 at http://apps.who.int/trialsearch/default.aspx.

Introduction

Monitoring the partial pressure of carbon dioxide (PCO_2) is an essential means of assessing alveolar ventilation in patients with chronic hypercapnic respiratory failure (HRF), particularly in those receiving nocturnal non-invasive positive pressure ventilation (NPPV), which is aimed at improving for improved alveolar hypoventilation and sleep quality.[1—12] Although the measurement of arterial PCO_2 ($PaCO_2$) is regarded as the gold standard technique for PCO_2 assessment[3,13—16] it is an invasive and painful method requiring an arterial blood gas analysis (ABG) or, alternatively, a blood sample from the arterialized ear lobe.[16] Importantly, it also disrupts a patient's sleep structure if performed during the night, and only reflects a snap shot of the potentially varying ventilatory status of patients with chronic HRF.[14,15,17—20] Although the relevance of $PaCO_2$ assessment is undisputed for several conditions, including acute respiratory failure,[21] non-invasive and continuous PCO_2 monitoring is clearly preferable for monitoring the varying status of alveolar ventilation during sleep.[2,5,9,15]

In general, two different techniques for continuous non-invasive PCO_2 monitoring have been introduced into clinical practice; namely, end-tidal ($PetCO_2$) and transcutaneous ($PtcCO_2$) measurements.[9,17,20] However, according to an early study, neither $PetCO_2$ nor $PtcCO_2$-monitoring provided an accurate reflection of $PaCO_2$ during sleep.[15] $PetCO_2$ monitoring is known to have limitations in parenchymal lung disease and, importantly, also in the case of air leakage around the mask or via mouth, which regularly occurs in NPPV patients.[3,7,15,17,20,22,23] In contrast, $PtcCO_2$-monitoring is independent from both air leakage and the underlying disease, and has been shown to be more reliable than $PetCO_2$ monitoring in different conditions.[24—27]

An important limitation of $PtcCO_2$-monitoring is the reported occurrence of technical $PtcCO_2$ drifts, which can be particularly momentous if monitoring is performed over a period of several hours or throughout the whole night.[5,17] Interestingly, more recent daytime studies have reported a substantial improvement in $PtcCO_2$ drifts, likely due to technical refinements in $PtcCO_2$-monitoring[13,14,28—34]; however, overnight studies using modern techniques are still lacking.

Therefore, if continuous and non-invasive overnight $PtcCO_2$-monitoring are determined to be just as accurate as invasive, intermittent $PaCO_2$-measurements, this technique could become the preferred means for monitoring nocturnal alveolar ventilation in chronic HRF patients. Hence, the present study aims to assess the accuracy of modern technologies designed for $PtcCO_2$-monitoring in patients receiving overnight NPPV. Some of the results of these studies have been previously reported in the form of an abstract.[35]

Materials and methods

The study protocol was approved by the Institutional Review Board for Human Studies at the Albert-Ludwigs University, Freiburg, Germany, and was performed in accordance with the ethical standards laid down in the Declaration of Helsinki. Written informed consent was obtained from all subjects.

Patients

Stable NPPV patients without evidence of acute respiratory failure and severe obesity (BMI > 35 kg/m^2) were included in this study[23,36] [for details see Supplementary Material].

Measurements

Lung function parameters (Masterlab-Compact® Labor; Jaeger; Hochberg, Germany) were assessed in accordance with international guidelines.[37—39] Daytime ABG samples (AVL OMNI®; Roche Diagnostics GmbH; Graz, Austria) were taken simultaneously from both the radial artery and the arterialized earlobe during spontaneous breathing at 4pm. Patients were excluded from the study if the ABG samples each taken from the artery and the arterialized earlobe showed a $PaCO_2$ difference >2.5 mmHg.[16]

$PtcCO_2$ was monitored using the latest generation of three different devices, with the sensor temperature set to 42 °C[20,31,34,40]: 1) SenTec Digital Monitor (SenTec DM, Software 06.21.1, V04.04.04; SenTec AG; Therwil, Switzerland), 2) TCM4-TINA (Version 2.12; Radiometer Medical ApS; Brønshøj, Denmark) and 3) TOSCA500 (Main 1.30; Radiometer Medical ApS). Full polysomnography (SOMNOscreen™ plus; Somnomedics GmbH; Randersacker, Germany) was performed according to guidelines[41—43] [for details see Supplementary Material].

Study design

All $PtcCO_2$-monitors were activated and calibrated 4 h prior to the sleep study. For nocturnal measurements the sensors of all three $PtcCO_2$-monitors were placed 5 cm below either the right or left clavicle with fixation rings. All three sensors were placed under the same clavicle. Lateral to medial positioning of the three sensors was chosen in a randomized

order, maintaining a distance of 5 cm. $PtcCO_2$ was monitored continuously with all devices simultaneously from 10.30pm to 7am, while sleep studies were also performed. Capillary ABG samples were intermittently taken at 11pm, 2am, 5am and 7am. Drift correction was performed immediately after the conclusion of measurements at 7am [for details see Supplementary Material].

Statistics

Statistical analysis was performed using a statistical software package (Sigma-Plot, version 11; Systat Software, Inc; Point Richmond, CA). Normally distributed data are presented as mean ± standard deviation (SD) (Kolmogorov–Smirnov test), while non-normally distributed data are presented as median with interquartile range.

Comparison between different patient groups was performed using the *t*-test for normally distributed data and the Mann–Whitney Rank Sum Test for not normally distributed data. The difference in technical calibration drifts[14] between SenTec DM, TCM4-TINA and TOSCA500 at the end of overnight $PtcCO_2$-monitoring was calculated using the Friedman Repeated Measures Analysis of Variance (RM-ANOVA) on Ranks. The difference in the overnight PCO_2 range (maximal minus minimal value) between $PaCO_2$ and drift-uncorrected $PtcCO_2$ by SenTec DM, TCM4-TINA and TOSCA500 was calculated using the Friedman Repeated Measures Analysis of Variance (RM-ANOVA) on Ranks.

Correlation analysis[44] and agreement in method comparison[45] between $PaCO_2$ and $PtcCO_2$ was performed using the methods described by Bland and Altman for each monitor, respectively. A difference of $\leq \pm 7.5$ mmHg between $PtcCO_2$ and $PaCO_2$ has been deemed acceptable.[28] Since previous studies reported a lower accuracy of $PtcCO_2$ in hypercapnic $PaCO_2$-ranges,[13,32,33] an analysis of method agreement for all hypercapnic $PtcCO_2/PaCO_2$–pairs of values (defined as $PaCO_2$ >50 mmHg) was performed. Statistical significance was assumed with a *p*-value of <0.05.

Results

A total of thirty consecutive patients were screened. Four of them showed a >2.5 mmHg discrepancy between daytime arterial and capillary blood gas analysis, as defined above. Two patients dropped out due to technical problems caused by staff. Therefore, 24 patients completed the study (Table 1). Fifteen patients had an underlying diagnosis of COPD. Nine patients had restrictive ventilatory disorders (non-COPD) due to amyotrophic lateral sclerosis ($N = 3$), pulmonary fibrosis, neuropathy, obesity hypoventilation syndrome, kyphoscoliosis, pneumectomy and congenital central hypoventilation syndrome ($N = 1$, respectively). Twenty-one patients received high-intensity NPPV in the assist/controlled mode as previously described,[11,12] and three patients received pressure support ventilation (Table 2). Results of polysomnography are presented in Table 2. Technical drift analysis and results of continuous overnight $PtcCO_2$-monitoring are given in Table 3. Here, the SenTec DM produced a smaller technical calibration drift after 8 h compared to TCM4-TINA and TOSCA500, while TCM4-TINA and TOSCA500 did not differ (RM-ANOVA, $p < 0.001$; Table 3). The mean technical drift per hour was calculated to be 0.1 mmHg for the SenTec DM, −0.4 mmHg for the TCM4-TINA and −0.5 mmHg for the TOSCA500, respectively. Results of correlation analysis and method comparison by Bland and Altman of $PtcCO_2/PaCO_2$–pairs are summarized in Table 4. Device related plots of method comparison are assessable for both drift-corrected and drift-uncorrected $PtcCO_2/PaCO_2$–pairs in the Supplementary Material Figs. 1–6.

Method comparison in the subgroup of $PtcCO_2/PaCO_2$-pairs with $PaCO_2$ >50mmHg ($N = 32$) revealed for drift-uncorrected values a mean bias (limits of agreement) of 2.1 (−3.1 to 7.3) mmHg for the SenTec DM, −1.3 (−15.7 to 13.2) mmHg for the TCM4-TINA, and 3.2 (−4.6 to 11.0) mmHg for the TOSCA500. For drift-corrected values a mean bias of 2.4 (−3.1 to 8.0) mmHg for the SenTec DM, −2.7 (−14.2 to 8.8) mmHg for the TCM4-TINA, and 0.5 (−6.7 to 7.8) mmHg for the TOSCA500 was calculated.

The four overnight capillary $PaCO_2$ values ranged by a median of 6.3 (4.7–9.7) mmHg, while the corresponding simultaneously monitored values for $PtcCO_2$ values ranged by a median of 5.8 (3.4–7.6) mmHg for the SenTec DM, 9.0 (6.0–12.0) mmHg for the TCM4-TINA and 6.5 (4.5–7.5) mmHg for the TOSCA500 (RM-ANOVA, $p = 0.003$; Fig. 1). Continuous overnight $PtcCO_2$ measurements revealed carbon dioxide ranges of 12.3 (10.7–14.5) mmHg for the SenTec DM, 14.5 (12.5–17.0) mmHg for the TCM4-TINA and 11.5 (11.0–13.0) mmHg for the TOSCA500 (RM-ANOVA, $p < 0.001$; Fig. 2). The overnight trend for $PaCO_2$ and $PtcCO_2$ values in a 34-year old patient with congenital central hypoventilation syndrome is displayed in Fig. 3.

Of the twenty-four patients measured, there was only one case for each $PtcCO_2$-monitor in which complete disconnection of $PtcCO_2$-Sensors occurred, thus requiring reattachment to the skin. Short-term intervals of missing data due to sensor detachment from the skin (but without need for sensor-replacement) were observed once each with the SenTec DM and TOSCA500 (Fig. 3), and three times with the TCM4-TINA.

Discussion

This is the first study analyzing the usefulness of modern techniques developed for non-invasive and continuous $PtcCO_2$-monitoring when applied during an 8-h-overnight period in patients receiving nocturnal NPPV to treat chronic HRF. There are two major findings arising from this study.

Firstly, all $PtcCO_2$-monitors investigated showed low technical drifts during the complete sleep study. Here, the minimal and maximal technical calibration drift was observed using the SenTec DM and TOSCA500, with an hourly $PtcCO_2$ value of 0.1 mmHg and −0.5 mmHg, respectively. This is in contrast to previous findings, where the technical drift was reported to be considerably higher, with values of 1.3 mmHg[14] and 1 mmHg[32] per hour. For this reason, the current data suggest a notable technical improvement in modern $PtcCO_2$-monitoring, with a substantial reduction in technical drift that allows reliable clinical application, even over long periods of 8 h.[17]

Secondly, when comparing nocturnal $PtcCO_2$-monitoring with the gold standard $PaCO_2$-measurements, the overall

Table 1 Demographic data, lung function parameters and arterial daytime blood gases. Values for mean ± standard deviation or median with interquartile range are given.

	COPD ($N = 15$)	NON-COPD ($N = 9$)	Difference of mean 95% CI	p-value
Male/female	10/5	6/3		
Age (years)	63.0 (56.3–71.5)	60.0 (45.0–70.0)	NF	0.283
BMI (kg/m^2)	25.3 ± 5.5	27.2 ± 4.5	−2.6 to 6.4	0.401
NPPV use (months)	6.0 (2.0–15.8)	90.0 (18.5–111.8)	NF	0.003
FEV_1 (% predicted)	22.2 (20.2–44.9)	45.6 (38.5–56.4)	NF	0.042
FVC (% predicted)	53.7 ± 19.8	50.8 ± 15.0	−19.6 to 13.9	0.724
FEV_1/FVC (%)	50.0 ± 13.1	83.6 ± 8.7	22.8 to 44.5	0.001
RV (% predicted)	257.7 (165.4–299.2)	91.9 (81.0–122.1)*	NF	0.002
TLC (% predicted)	113.1 ± 22.1	64.1 ± 8.9*	−67.2 to −30.6	<0.001
LTOT (L/min)	2.0 (1.0–3.0)	0.0 (0.0–1.1)	NF	0.067
pH	7.41 ± 0.03	7.42 ± 0.02	−0.02 to 0.03	0.519
$PaCO_2$ (mmHg)	47.7 ± 7.8	45.1 ± 7.3	−9.4 to 4.2	0.430
PaO_2 (mmHg)	76.3 (60.6–94.1)	75.2 (69.8–85.4)	NF	0.975
HCO_3^- (mmol/l)	29.5 ± 3.2	28.6 ± 4.4	−4.2 to 2.4	0.579
BE (mmol/l)	4.4 ± 2.2	3.9 ± 3.5	−3.0 to 2.0	0.705

BE = base excess, BMI = body mass index, CI = confidence interval, FEV_1 = forced expiratory volume in 1 s, FVC = forced vital capacity, HCO_3^- = standard bicarbonate, LTOT = long-term oxygen therapy, NF = normality test failed, $PaCO_2$ = arterial partial pressure of carbon dioxide, PaO_2 = arterial partial pressure of oxygen, RV = residual volume, TLC = total lung capacity. *$n = 8$.

differences were low. This supports $PtcCO_2$-monitoring as a useful means of monitoring nocturnal alveolar ventilation. Previous studies have already compared these two techniques in NPPV patients[13,31–33]; however, most studies were performed during the day and an entire sleep study was not included in any of these trials. In addition, only a low number of $PaCO_2$/$PtcCO_2$-pairs were included in the analysis.

In an initial daytime trial, the range in limits of agreement was reported to be 11 mmHg in 26 $PaCO_2$/

Table 2 NPPV settings and polysomnography during nocturnal NPPV. Values for mean ± standard deviation or median with interquartile range are given.

	COPD ($N = 15$)	NON-COPD ($N = 9$)	Difference of mean 95% CI	p-value
NPPV settings				
Mask: nasal/full face	6/9	6/3		
Oxygen flow (L/min)	3.0 (2.0–3.0)	0.0 (0.0–1.1)	NF	0.002
IPAP (mbar)	28.0 (24.3–29.5)	20.0 (17.8–23.2)	NF	0.023
EPAP (mbar)	4.0 (4.0–5.0)	4.0 (1.5–5.0)	NF	0.591
RR_{set} (/min)	20.0 (18.0–20.0)	18.0 (14.8–20.5)	NF	0.654
Inspiratory Time (sec)	1.0 (1.0–1.0)[a]	1.3 (1.1–1.3)[b]	NF	0.011
Polysomnography				
TST (min)	283.1 ± 108.1	284.4 ± 47.7[c]	−82.9 to 85.9	0.976
Sleep efficiency (%)	78.6 (62.9–82.0)	83.9 (67.1–84.5)[c]	NF	0.259
NREM 1 (% TST)	18.5 (10.2–22.9)	24.7 (8.5–38.5)[c]	NF	0.478
NREM 2 (% TST)	47.5 ± 19.5	49.5 ± 16.8[c]	−14.9 to 18.9	0.809
NREM 3 + 4 (% TST)	15.2 ± 10.0	13.4 ± 6.8[c]	−10.0 to 6.5	0.666
REM (% TST)	13.1 ± 9.0	9.5 ± 6.2[c]	−11.0 to 3.8	0.321
Arousals (/h)	19.4 ± 15.3	19.7 ± 10.3[c]	−12.3 to 12.9	0.963
Apnea-Hypopnea-Index (/h)	0.8 (0.3–6.7)	1.8 (0.5–9.9)	NF	0.189
Mean SaO_2 (%)	91.7 ± 3.1	92.3 ± 2.5	−1.8 to 3.2	0.587
Desaturation-Index (/h)	1.4 (0.8–5.7)	1.3 (0.5–10.4)	NF	0.743
Heart rate (/min)	73.5 ± 10.2	68.9 ± 13.1	−14.5 to 3.2	0.341

EPAP = expiratory positive airway pressure, IPAP = inspiratory positive airway pressure, NF = normality test failed, NPPV = non-invasive positive pressure ventilation, NREM = non-rapid eye movement sleep, REM = rapid eye movement sleep, RR_{set} = preset respiratory rate (including back-up frequency in pressure support mode), SaO_2 = oxygen saturation, TST = total sleep time.

[a] $N = 13$.

[b] $N = 8$ since two COPD- and one NON-COPD-patient(s) received pressure support ventilation.

[c] $n = 8$ since one patient underwent polygraphy instead of polysomnography.

Table 3 Continuous overnight $PtcCO_2$-monitoring. Median (interquartile range) is given for all patients ($N = 24$), irrespective of the underlying disease.

	SenTec DM	TCM4-TINA	TOSCA500	*p*-value (RM-ANOVA)
Technical Drift (mmHg)	0.7 (−0.2 to 1.7)	−4.0 (−5.0 to −2.0)	−4.0 (−6.0 to −2.5)	<0.001
Mean of overnight $PtcCO_2$ (mmHg)	48.5 (42.4−50.6)	47.9 (43.6−59.0)	47.8 (42.9−49.8)	0.718
Standard deviation of overnight $PtcCO_2$ (mmHg)	2.5 (1.9−3.0)	3.2 (2.3−4.0)	2.4 (2.1−3.0)	0.121

$PtcCO_2$ = transcutaneous partial pressure of carbon dioxide.

$PtcCO_2$−pairs.[13] In a further 8-h-daytime-study the range in limits of agreement was 15 mmHg (28 $PaCO_2$/$PtcCO_2$−pairs).[31] Furthermore, twelve patients were analyzed over a 40min period of daytime NPPV. Here, the analysis of 48 pairs of values revealed a 12 mmHg range in limits of agreement.[33] The sole overnight study assessed the first 5 h of the night with two different $PtcCO_2$-monitors in ten NPPV patients.[32] Unfortunately, no comparison according to the methods proposed by Bland and Altman[45] was performed in that study. In clear contrast, the present study is the first to use modern $PtcCO_2$-monitoring techniques to describe complete overnight $PtcCO_2$-monitoring, with high-standard Bland and Altman statistical analysis. Thereby, the range in limits of agreement was dependent on the device being used, with the lowest range value of 11.4 mmHg from the SenTec DM monitor deemed acceptable for the purpose of overnight monitoring of alveolar ventilation in patients with chronic HRF.

In most of the previous studies method comparison revealed inconsistent results when comparing hypercapnia to normocapnic conditions.[31−33] The current study did not focus on acute ventilatory failure or extremely hypercapnic patients. However, in contrast to the afore mentioned findings,[31−33] the present study demonstrated that method comparison was not inferior in hypercapnic values above 50mmHg suggesting an improvement of the technology in the hypercapnic range. Furthermore, it remains speculative if the current findings are transferable to extremely obese patients suffering from obesity hypoventilation syndrome, which are suggested to be the major subgroup receiving NPPV in the future.[7] Adipose tissue may have an impact on $PtcCO_2$-measurment. However, since previous studies[7,14,33] including more obese patients reported similarly positive results in $PtcCO_2$-monitoring it is likely that monitoring of more obese patients is feasible with a comparable quality.

In addition, pairs of values outside the clinically acceptable range of >7.5 mmHg[28] were rare in two of the applied monitors (SenTec DM 1% and TOSCA500 2% for drift-uncorrected $PtcCO_2$ values, respectively). This is in contrast with an earlier intensive care unit study, where 19% of measured pairs were beyond this range.[28] These findings indicate that $PtcCO_2$-monitoring is a robust method for nocturnal application. Although the present study did not aim to directly compare modern and older techniques

Table 4 Correlation analysis and method comparison of $PtcCO_2$/$PaCO_2$-pairs at 11 pm, 2 am, 5 am and 7 am. Results are given for all patients ($N = 24$), irrespective of the underlying disease.

	SenTec DM	TCM4-TINA	TOSCA500
$PaCO_2$ versus drift-uncorrected $PtcCO_2$			
Pairs of values (N)	93	88	92
Pearson correlation coefficient (R), *p*-value	$R = 0.943$, $p < 0.001$	$R = 0.740$, $p < 0.001$	$R = 0.901$, $p < 0.001$
Mean of the difference (mmHg)	1.0	−1.5	0.8
Limits of agreement (range) (mmHg)	−4.7 to 6.7 (11.4)	−15.6 to 12.5 (28.1)	−6.8 to 8.3 (15.1)
Mean of the difference >7.5 mmHg	1.1%	27.3%	2.2%
$PaCO_2$ versus drift-corrected $PtcCO_2$	software based	calculated	calculated
Pairs of values (N)	90	80	92
Pearson correlation coefficient (R), *p*-value	$R = 0.946$, $p < 0.001$	$R = 0.775$, $p < 0.001$	$R = 0.922$, $p < 0.001$
Mean of the difference (mmHg)	0.8	−3.3	−1.6
Limits of agreement (range) (mmHg)	−4.9 to 6.5 (11.4)	−15.8 to 9.3 (25.1)	−8.4 to 5.2 (13.6)
Mean of the difference >7.5 mmHg	1.1%	28.8%	4.3%

$PaCO_2$ = arterial partial pressure of carbon dioxide, $PtcCO_2$ = transcutaneous partial pressure of carbon dioxide.

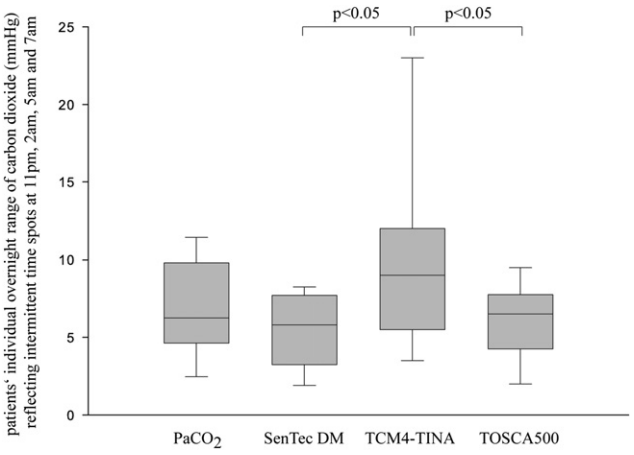

Figure 1 Range of overnight carbon dioxide measurements of $PaCO_2$ and simultaneously monitored $PtcCO_2$ reflecting intermittent time spots at 11pm, 2am, 5am and 7am ($N = 24$; RM-ANOVA, $p = 0.003$). $PaCO_2$ = arterial partial pressure of carbon dioxide, $PtcCO_2$ = transcutaneous partial pressure of carbon dioxide by SenTec DM, TCM4-TINA and TOSCA500.

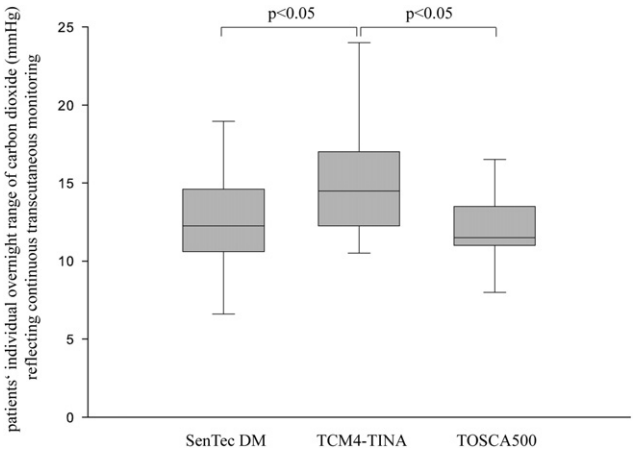

Figure 2 Range of overnight carbon dioxide measurements reflecting continuous transcutaneous monitoring ($N = 24$; RM-ANOVA, $p < 0.001$). $PaCO_2$ = arterial partial pressure of carbon dioxide, $PtcCO_2$ = transcutaneous partial pressure of carbon dioxide by SenTec DM, TCM4-TINA and TOSCA500.

of $PtcCO_2$-monitoring, the improvements in the stability and reliability of $PtcCO_2$-monitoring are likely attributed to further technical refinements of the monitors.

It is well accepted that alveolar ventilation varies during sleep in chronic HRF patients.[5,34,46] Thereby, previous studies have explicitly demonstrated that when NPPV is applied during sleep, inspiratory, expiratory and leak volumes vary substantially in individual patients.[7,12,22,23,47,48] Accordingly, the current study has shown that the range of overnight PCO_2 is higher when assessed by all three continuous $PtcCO_2$-monitors (Fig. 2) compared to intermittent PCO_2 assessment (Fig. 1), even if ABG is performed four times during night, which is more frequent than what is usually done in clinical practice.[3,9,10,12,22,32,49] In line with these findings considerable nighttime fluctuations of PCO_2 due to various events as given in Fig. 3 are only detectable by a continuous assessment as given by $PtcCO_2$ and would have been missed relying on single morning blood gas analysis. Thus, there is clear evidence that continuous monitoring of alveolar ventilation using $PtcCO_2$-monitoring is by far more comprehensive than the single, random assessments provided by intermittent $PaCO_2$-measurments. In addition, while intermittent ABG is invasive and sleep-disrupting,[9] $PtcCO_2$-monitoring is not likely to affect sleep quality because it is non-invasive; once the sensor has been adjusted prior to falling asleep, there is no need for specific maneuvers during night. Based on these considerations and also on the increasing reliability and stability of $PtcCO_2$-monitoring, the current authors propose $PtcCO_2$-monitoring to be the preferred method for monitoring alveolar ventilation during nocturnal NPPV in chronic HRF patients.

However, in contrast to SenTec DM and TOSCA500, the TCM4-TINA monitor displayed expanded individual ranges and wider limits of agreement for $PtcCO_2$-monitoring compared to $PaCO_2$. This might be attributed to the sensor temperature of 42 °C, since higher temperatures were recently reported to produce more acceptable limits of agreement for the TCM4-TINA compared to $PaCO_2$.[27,33,40] While higher temperatures might be reasonable for short-term $PtcCO_2$-monitoring, such as during endoscopies,[17,50] higher sensor temperatures can cause cutaneous side-effects during longer application, which is unacceptable for overnight sleep studies.[17,20,31] In addition, differences in sensor membrane and changing frequency might be a reason for divergence comparing results of TCM4-TINA to SenTec DM or TOSCA500.

For nighttime measurements of capillary ABG patients were not actively woken. However, due to the procedure of ABG sleep quality was very likely to be negatively affected

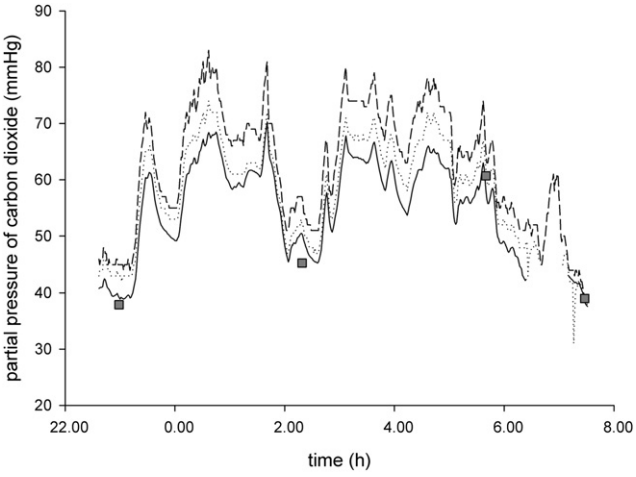

Figure 3 Overnight trend of $PaCO_2$ (grey boxes) and $PtcCO_2$ (solid line represents SenTec DM, interrupted line represents TCM4-TINA, and dotted line represents TOSCA500) during non-invasive positive pressure ventilation in a 34-year old patient with congenital central hypoventilation syndrome showing nighttime fluctuations of PCO_2. The sensors were disconnected from the patient between 6.30am and 7am for SenTec DM and TOSCA500. $PaCO_2$ = arterial partial pressure of carbon dioxide, $PtcCO_2$ = transcutaneous partial pressure of carbon dioxide.

by arousals.[9] Furthermore, a lag time of $PtcCO_2$-monitoring influencing method comparison to $PaCO_2$ could not be excluded. As we showed in a previous work, the $PtcCO_2$ value monitored with a 2 min delay was the best predictor of $PaCO_2$ compared to the simultaneously and 5-min delayed monitored $PtcCO_2$ value.[14] However, $PtcCO_2$ monitored simultaneously to $PaCO_2$ is suggested to be a good predictor as well,[14] and it remains speculative if an overnight study taking into account the lag time would lead to further improvement in method comparison of $PaCO_2$ and $PtcCO_2$.

Any technical problems arising during $PtcCO_2$-monitoring were manageable throughout the study. Short-term, intermittent sensor detachment with associated data loss was evident once each with the SenTec DM and TOSCA500, and three times with the TCM4-TINA. The higher incidence of sensor detachment with the TCM4-TINA might be attributed to differences in the sensor fixation rings. While the TCM4-TINA is wound into the fixation ring, the SenTec DM and TOSCA500 each use a click-on ring which allows free rotation. Following the above mentioned divergence in results of TCM4-TINA to SenTec DM and TOSCA500 a free sensor rotation might be an advantage in method comparison of $PtcCO_2$ to $PaCO_2$. However sensor reattachment following complete sensor disconnection was rarely required, occurring only once for each of the three transcutaneous monitors. In addition, there was no need for recalibration of the monitors during the night.

In conclusion, calibration drifts in transcutaneous PCO_2 values and the differences between transcutaneous and arterial PCO_2 have been shown to be low when modern monitors are used to assess transcutaneous PCO_2. Thus, overnight $PtcCO_2$-monitoring has become a reliable and robust tool for assessing alveolar ventilation during sleep in chronic HRF patients receiving NPPV. Furthermore, $PtcCO_2$-monitoring is non-invasive, and provides a more complete picture of nocturnal alveolar ventilation. Given that intermittent nocturnal arterial blood gas analysis disrupts sleep quality and provides only a highly selective account of alveolar ventilation during the night, the time has now come to consider modern, technically-improved transcutaneous PCO_2 monitoring as the new gold standard for nocturnal monitoring of alveolar ventilation in chronic HRF patients with NPPV.

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.rmed.2010.10.007.

Conflict of interest statement

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